

## REMARKS

Claims 1, 3, 5 and 7-16 are pending in the application. Claims 1, 3 and 5 have been amended to recite SEQ ID NO:7 rather than SEQ ID NO:2. Support for the amendment can be found, *inter alia*, at page 26, lines 28-32. No new matter has been added. Reconsideration is requested.

The Examiner indicated that claim 3 was allowed. It is respectfully submitted that claim 3, as amended, should be allowable. Reconsideration of claims 1, 5, and 7-16 in view of the following remarks is respectfully requested.

### Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 5 and 7-16 were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure without evidence that the claimed vaccine and method produce a protective immune response. Applicants previously submitted the Declaration of Dr. Jeffrey Lyon, one of the inventors on the application, in support of the invention as claimed. The Declaration presented challenge data in Aotus monkeys. Animals underwent a series of vaccine injections with a vaccine according to the invention, and were subsequently challenged by exposure to the FVO strain of *P. falciparum*. The vaccine of the invention produced a significant reduction in infection by *P. falciparum*, as shown in Figure 2 of the Declaration. (It is noted that due to a typographical error, the previous amendment improperly indicated "Figure 3".)

It is the Examiner's position that the Declaration is not commensurate in scope with the specification and claims.

First, the Examiner stated that it is not clear what the GMP protein is, and that it is not clear that SEQ ID NO:2 as claimed is the same as FMP-1 or GMP protein. Applicants confirm that GMP protein as discussed in the Declaration is the same as FMP-1. GMP refers to "Good Manufacturing Practice", as is well known in the art, and is referred to at several places in the specification. As noted in item 6 of the Declaration, the protein referred to as FMP-1 was manufactured according to the method described in the patent application at pages 52-55. This

corresponds to SEQ ID NO:7, as noted, *inter alia*, at page 31, lines 4-6, of the application. The claims have been amended to refer to SEQ ID NO:7.

The MSP1<sub>42</sub> gene fragment from the 3D7 strain of *Plasmodium falciparum* was expressed as soluble protein in *Escherichia coli* and purified according to Good Manufacturing Practice (GMP) specifications, and according to the method described in the patent application at pages 52-55. This recombinant protein is referred to as FMP1. The FMP1 protein was reactive with several functional, conformation-dependent monoclonal antibodies raised against *P. falciparum* malaria parasites (Angov, E., B. M. Aufiero, A. M. Turgeon, M. Van Handenhove, C. F. Ockenhouse, K. E. Kester, D. S. Walsh, J. S. McBride, M. C. Dubois, J. Cohen, J. D. Haynes, K. H. Eckels, D. G. Heppner, W. R. Ballou, C. L. Diggs, and J. A. Lyon. 2003. Development and pre-clinical analysis of a *Plasmodium falciparum* merozoite surface protein- (42) malaria vaccine. Mol. Biochem.Parasitol. 128:195–204). Among these are several functional mAb that were raised against red cells infected with mature *P. falciparum* parasites.

Second, the Examiner states that the specification does not set forth that Aotus monkeys do not get infected with 3D7 and get infected with FVO. This is well known in the art, and in any event it is not clear why it would be required to be disclosed in the specification. It is respectfully submitted that the demonstration of efficacy in Aotus monkeys is sufficient to overcome the rejection. Claim 5, for example, recites "A method for inducing a protective immune response to malaria in a **mammal**, comprising... administering a composition... in an amount effective to induce an immune response in said **mammal**...". Applicants' Declaration demonstrates that the claimed vaccine and method does induce an immune response and reduces parasitaemia levels in Aotus monkeys, a **mammal**.

As noted by the Examiner, the specification discloses that Rhesus monkeys were immunized with the claimed composition, which induced an antibody response. The Examiner states that Kumar et al. disclosed the composition FVO MSP-1<sub>42</sub> to immunize Aotus monkeys and challenged with FVO, and that this would read on the claimed invention. Applicants have previously explained in detail the differences between the claimed invention and the compositions of Kumar et al. It is widely known in the art that Aotus monkeys can be vaccinated

to test the efficacy of a malaria vaccine. However, the MSP1-42 composition of Kumar et al. was not effective. It is noted that the Examiner has not made a 35 USC § 102 or § 103 rejection.

The Examiner stated that the examples in the specification used Rhesus monkeys, while the Declaration presents results using Aotus monkeys. However, the invention is not limited to any particular species, nor do the claims recite a vaccine or method to be limited to monkeys, let alone any particular species of monkeys. The results presented in the Declaration show that when Aotus monkeys are immunized with the compositions of the invention, they develop a protective immune response to malaria, evidenced by decreased parasitemia. As noted above, Aotus monkeys are an art-recognized model for testing erythrocytic-stage malaria vaccines. It is respectfully submitted that this evidence fully demonstrates that the claimed invention is enabled.

Third, the Examiner states that adjuvant AS02A is not described in the specification or the claims. AS02A corresponds to the adjuvant specified in claim 13, although it is not specifically identified as AS02A in the specification. AS02A is SBAS2 that has been manufactured without thimerisol (see Ballou, et. al. Am. J. Trop. Med. Hyg., 71(Suppl 2), 2004, pp. 239–247). SBAS2 emulsion is prepared by adding 5 µg MPL and 5 µg QS21 per dose to SB62 emulsion (as described in US Patents 6,706,270 and 6,544,518). SB62 emulsion is described in US Patent 6,623,739. It is prepared by emulsifying 5% Squalene 5% tocopherol 2.0% tween 80; the particle size in the emulsion is 180 nm. The SB6 emulsion containing 5 µg MPL and 5 µg QS21 per dose is specified in claim 13. It is respectfully submitted that AS02A is an art-recognized adjuvant and is disclosed in the specification.

Fourth, the Examiner states that "[t]he Declaration indicates that the claimed composition inhibits parasitaemia and thereby can be used in a method to inhibit or treat parasitaemia caused by *Plasmodium falciparum*. Therefore, the rejection is maintained." This statement is not understood. Parasitaemia is the presence of parasites in the peripheral circulation. As noted by the Examiner, the specification defines vaccine as an immunogenic composition capable of eliciting protection against malaria, whether partial or complete (specification, page 23). It is respectfully submitted that the reduction of parasitemia would be considered at least partially protective against malaria by those of skill in the art.

The Examiner appears to take the position that a therapeutic vaccine is a "therapeutic agent...used in the prevention, alleviation, treatment or cure of disease", and that the animal(s) to whom the vaccine was administered in the present application was "merely a bioreactor", and that therefore the recited composition is not a vaccine. Applicants respectfully disagree. While the claimed vaccine was administered to certain test animals that are not susceptible to malaria (e.g. mice) to determine various biological properties, it was also tested in Aotus monkeys, as described in the Declaration of Dr. Lyon, under conditions where it clearly alleviated parasitemia resulting from malaria infection. Accordingly, it is respectfully submitted that the claimed vaccine and method meet the Examiner's requirements as "therapeutic" and "alleviation...of disease".

The specification also states "The objective of an erythrocyte stage vaccine is to diminish the level of parasitemia in the bloodstream and thus reduce the severity of disease." (page 2, line 10). Therefore, if the claimed composition inhibits (alleviates) parasitemia, it functions as a vaccine and method as claimed. As detailed in the Declaration, these requirements have clearly been met.

Furthermore, point 7 of the Declaration clearly states that it is the expert opinion of Dr. Lyon that the vaccine made as described in the specification has a protective effect against infection by a heterologous strain of *Plasmodium falciparum*.

In view of the above, it is respectfully submitted that the Declaration of Dr. Lyon clearly demonstrates that the present claims are enabled. Reconsideration and withdrawal of the 35 USC § 112, first paragraph rejection are respectfully requested.

Lyon et al. -- Appl. No. 10/057,532

All objections and rejections having been addressed, it is respectfully requested that the rejections be withdrawn and a Notice of Allowance issued. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Respectfully submitted,

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